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Liquid chromatography–electrospray mass spectrometry determination of carbamazepine, oxcarbazepine and eight of their metabolites in human plasma

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Abstract

Carbamazepine (CBZ) and oxcarbazepine (OXCBZ) are both antiepileptic drugs, which are prescribed as first-line drugs for the treatment of partial and generalized tonic–clonic epileptic seizures. In this paper, a specific and sensitive liquid chromatography–electrospray ionization mass spectrometry method was described for the simultaneous determination of carbamazepine (CBZ), oxcarbazepine (OXCBZ) and eight of their metabolites [CBZ-10,11-epoxide (CBZ-EP), 10,11-dihydro-10,11-*trans*-dihydroxy-carbamazepine (DiOH-CBZ), 10-hydroxy-10,11-dihydroCBZ (10-OH-CBZ), 2-hydroxycarbamazepine (2-OH-CBZ), 3-hydroxycarbamazepine (3-OH-CBZ), iminostilbene (IM), acridone (AO) and acridine (AI)] in human plasma. The work-up procedure involved a simple precipitation with acetone. Separation of the analytes was achieved within 50 min using a Zorbax eclipse XD8 C8 analytical column. The mobile phase consisted of a mixture of acetonitrile–formate buffer (2 mM, pH 3). Detection was performed using a quadrupole mass spectrometer fitted with an electrospray ion source. Mass spectrometric data were acquired in single ion recording mode at *m*/*z* 237 for CBZ, *m*/*z* 180 for CBZ-EP and AI, *m*/*z* 236 for OXCBZ, *m*/*z* 237 for 10-OH-CBZ, *m*/*z* 253 for 2-OH-CBZ, 3-OH-CBZ and DiOH-CBZ, *m*/*z* 196 for AO and *m*/*z* 194 for IM. For all analytes, the drug/internal standard peak height ratios were linked via a quadratic relationship to plasma concentrations. The extraction recovery averaged 90% for CBZ, 80% for OXCBZ and was 80–105% for the metabolites. The lower limit of quantitation was 0.5 mg/l for CBZ, 0.4 mg/l for OXCBZ and ranged from 0.02 to 0.3 mg/l for the metabolites. Precision ranged from 2 to 13% and accuracy was between 86 and 112%. This method was found suitable for the analysis of plasma samples collected during therapeutic drug monitoring of patients treated with CBZ or OXCBZ.

Keywords: Liquid chromatography–mass spectrometry; Carbamazepine; Oxcarbazepine; Metabolites; Validation

1. Introduction

Carbamazepine (5H-dibenz/bf/azepine-5-carboxamide) (CBZ) is the most frequently prescribed first-line drug for the treatment of partial and generalized tonic–clonic epileptic seizures [1]. Of the adverse reactions associated with CBZ, 5% can be classified as idiosyncratic or hypersensitivity reactions. These can range from serious skin reactions, such as erythema multiforme [2], to severe haematological disorders, especially agranulocytosis and aplastic anemia [3,4]. Such reactions are unpredictable and are associated with high mortality rates. Although the mechanism of CBZ-induced adverse reactions is not clear, they are thought to result from the formation of reactive metabolites [5].

Carbamazepine is predominantly metabolized in the liver into various metabolites. At least 30 different metabolites have been

Abbreviations: CBZ, carbamazepine; OXCBZ, oxcarbazepine; CBZ-EP, carbamazepine-10,11-epoxide; DiOH-CBZ, 10,11-dihydro-10,11-*trans*-dihydroxy-carbamazepine; 10-OH-CBZ, 10-hydroxy-10,11-dihydro carbamazepine; 2-OH-CBZ, 2-hydroxycarbamazepine; 3-OH-CBZ, 3-hydroxycarbamazepine; IM, iminostilbene; AO, acridone; AI, acridine; QC, quality control

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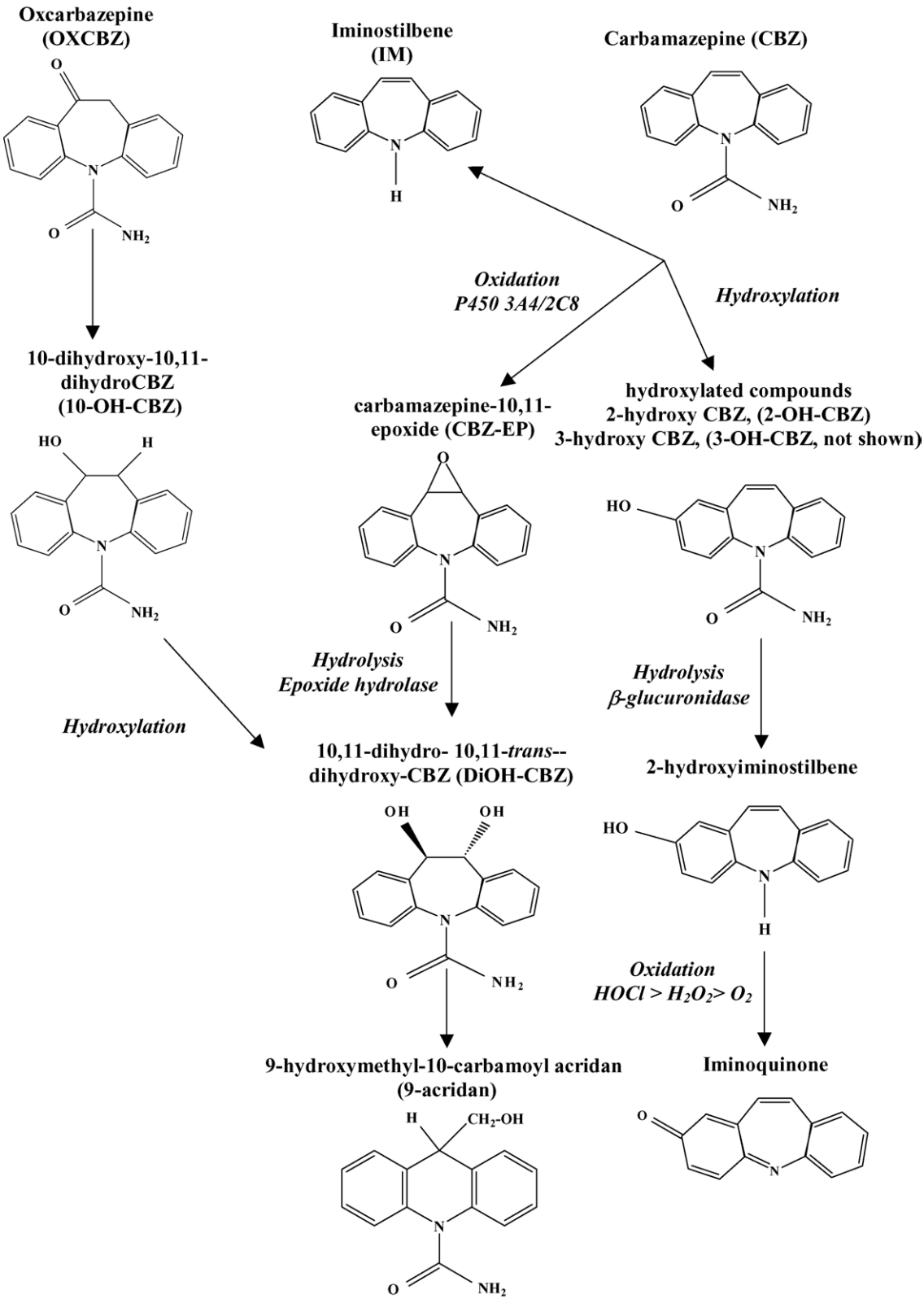

Fig. 1. Hepatic metabolism pathway of carbamazepine and oxcarbazepine. For the hydroxylated compounds, the hydroxylation in position 2 is only presented.

identified [6]. Three principal metabolic pathways have been described [7–13] (Fig. 1). The main route is the formation of the carbamazepine-10,11-epoxide (CBZ-EP), a pharmacologically active compound with anticonvulsant properties. A second route of metabolism concerns the production of hydroxylated compounds. The third minor route of metabolism leads to the formation of iminostilbene (IM). Although the liver is the major site of drug metabolism, the biological half-life of most reactive